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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/695,509	SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 28 October 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 1-19, as specifically drawn to a method of inhibiting tumor cells and/or cancer cells and or benign prostate hyperplasia, while reducing the risk of UV radiation exposure or vitamin D toxicity, said method comprising the steps of administering to a patient a composition comprising an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihydroxyvitamin D in said cells in a target organ, wherein the tumor cells have a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said metabolic precursor, are currently pending and under consideration.

Claim Objections

Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, dependent claim 7's limitation that the metabolic precursor is administered as a composition comprising said metabolic precursor, or a salt, isomer or derivative thereof does not appear to further limit independent claim 1 because claim 1 has already set forth administration of an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D and is silent on an isomer or derivative thereof.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 11-15 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. In the instant case, the claims are inclusive of a genus of metabolic precursors and derivatives thereof (claim 7) of 1,25-dihydroxyvitmain D. Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. However, the written description in this case only sets forth one species of metabolic precursors of 1,25-dihydroxybitamin D, wherein the metabolic precursor is 25-hydroxyvitamin D.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 17, lines 10-21) that one aspect on the invention is to administer an effective amount of a vitamin D metabolite which can be metabolically converted by the target cells by 1,25(OH)2D, wherein the vitamin D metabolite does not cause an increased risk of skin cancer (as compared to sun or ultraviolet (UV) ray exposure), vitamin D toxicity (as compared to supplemental excessive vitamin D administration, and does not significantly contribute to hypercalcemia (as compare to administering 1,25 (OH)2D). The specification further teaches Page 17, lines 21-22) that the preferred embodiment is an effective amount of 25 (OH)D, or an analog, derivative, salt, or functional equivalent thereof. With regards to the analogs or derivatives of 25(OH)D, the specification teaches that analogs and derivatives of 25(OH)D include, but are not limited to, alkylated, glycosylated, arylated, halogenated, or hydroxylated 25(OH)D, orthoesters of 25 (OH)D, wherein the vitamin D analogs can be obtained following the methods disclosed in a plethora of US. Patents (page 18, lines 25+). With regards to the "functional equivalent", the specification teaches that the term "functional equivalent" refers to any compound which can be used as a substrate for 1a-Ohase or other wise be converted to 1,25(OH)2D or converted to a compound which can bind to or activate the 1,25 (OH)2D receptor (VDR) (page 19, lines 10-16. Thus, while the specification contemplates any vitamin D metabolite and any derivative, analog or

functional equivalent of 25-(OH)D, e.g., 25-hydroxyvitamin D, the specification only reasonably conveys one species of metabolic precursors of 1,25-dihydroxyvitamin D, wherein the metabolic precursor is 25-hydrovitamin D. A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of metabolic precursors of 1,25-dihydroxyvitamin D that encompass the genus nor does it provide a description of structural features that are common to the precursors. Since the disclosure fails to describe the common attributes or characteristics that

identify members of the genus, and because the genus is highly variant, the disclosure of one species is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of metabolic precursors of 1,25-dihydroxyvitamin D, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only one species of metabolic precursors of 1,25-dihydroxybitamin D, wherein the metabolic precursor is 25-hydrovitamin D, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting colon, breast cancer cells and lymphoma comprising administering to a patient an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihyroxyvitmain D in said tumor cells in the target organ, wherein the tumor cells have 25-hydroxyvitmain D-1a-hydroxylase for synthesizing 1,25-dihyrovitamin D from

said metabolic precursor, does not reasonably provide enablement for a method of inhibiting any and/or all tumor cells comprising administering to a patient an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihyroxyvitmain D in said tumor cells in the target organ, wherein the tumor cells have 25-hydroxyvitmain D-1a-hydroxylase for synthesizing 1,25-dihyrovitamin D from said metabolic precursor or a method of treating benign prostatic hyperplasia in an animal, while reducing the risk of UV radiation exposure or Vitamin D toxicity, said method comprising administering a composition comprising an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihydroxyvitamin D in prostatic cells having a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said metabolic precursor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working

example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

Claims 1-14 are drawn to a method of inhibiting tumor cells/cancer cells comprising administering to a patient an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihyroxyvitmain D in said tumor cells in the target organ, wherein the tumor cells have 25-hydroxyvitmain D-1a-hydroxylase for synthesizing 1,25-dihyrovitamin D from said metabolic precursor. Claims 15-19 are drawn to a method of treating benign prostatic hyperplasia in an animal, while reducing the risk of UV radiation exposure or Vitamin D toxicity, said method comprising administering a composition comprising an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihydroxyvitamin D in prostatic cells having a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said metabolic precursor. As such, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of inhibiting any and/or all tumor cells including, but not limited to prostate cancer cells, breast cancer cells, skin cancer cells, pancreatic cancer cells, colon cancer cells, lung cancer cells, leukemia cell and lymphoma cells comprising administering to a patient an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihyroxyvitmain D in said tumor cells in the target organ, wherein the tumor cells have 25-hydroxyvitmain D-1a-hydroxylase for synthesizing 1,25-dihyrovitamin D from said metabolic precursormethod of treating benign prostatic hyperplasia in an animal, while reducing the risk of UV radiation exposure or Vitamin D toxicity, said method comprising administering a composition comprising an effective amount of a metabolic precursor of 1,25-dihydroxyvitamin D to increase levels of 1,25-dihydroxyvitamin D in prostatic cells having a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said metabolic precursor. As such, the claims imply that there is a correlation between the presence of a hydroxylase enzyme for synthesizing the active 1,25-dihyroxyvitamin D from a metabolic precursor and any tumor cell line or benign prostatic hyperplasia.

Guidance in the specification and Working Examples

The specification teaches that one aspect of the invention comprises increasing the local cellular levels of $1,25(OH)_2D$ by administering an effective amount of a Vitamin D metabolite which can be metabolically converted by the target cells to $1,25(OH)_2D$ for the prevention or treatment of cell proliferation, invasiveness, or metastasis (page 17, lines 10-15). For example, the speciation teaches that the subject method of administering a metabolic precursor of $1,25(OH)_2D$ to a patient has been shown to be successful in producing $1,25(OH)_2D$ by prostatic cancer cells and two primary culture of cells, NP96-5 and BPH96-11 (page 19, lines 21+). Moreover, the specification teaches that colon or breast cells have also been shown to possess 1α-OHase activity (page 25, lines 1-2). The specification further teaches that in one embodiment, a polynucleotide construct containing a gene that codes for 1a-OHase can be used to treat a cell exhibiting benign prostatic hyperplasia. Thus, while the specification teaches that 1α-OHase which is capable of synthesizing 1,25(OH)2D is present in two prostatic cancer cells lines, 1 BPH cell line and colon/breast cancer cells, the

specification appears to be silent on the presence of the hydrolase enzyme in any other cancer cell line and whether or not the synthesis of $1,25(OH)_2D$ from administration of a metabolic precursor may be used as an effective *in vivo* treatment of any and/or all cancers or benign prostate hyperplasia.

Quantity of experimentation

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that vitamin D3 undergoes hydroxylation first in the liver to form 25-hydroxyvitamin D3 which is further hydroxylated in the kidney by Vitamin D 1a-hydroxylse to create the biologically active form $1,25\ (OH)_2D3$ (Ma et al. Molecular and Cellualr Endocrinology 2004; 221: 67-74). With regards to $1,25\ (OH)_2D3$, Ma et al. teach that $1,25\ (OH)_2D3$ has been shown to inhibit established prostatic cancer cell lines as well as primary culture of normal and malignant prostatic epithelial cells (page 67, 2nd column last paragraph to page 68, 1st column). Despite the anti-tumor activity of $1,25\ (OH)_2D3$, Ma et al. teach that systemic hypercalcemia resulting from excessive circulation of $1,25\ (OH)_2D3$ has limited its therapeutic potential and has led investigators to propose new strategies to harness the anti-tumor activity of 1,25 (OH)2D3 while circumventing hypercalcemic activity. For example, Ma et al. teach that this discovery has raised the possibility of intra-prostatic conversion of 25(OH)D3 to 1,25(OH)2D3 by endogenous 1a(OH)ase, allowing the use of the less hypercalcermic 25(OH)D3 instead of 1,25(OH)2D3 as a therapeutic approach (page 68, 1st column, 2nd paragraph). However, Ma et al. teach that 1a(OH)ase activity in human prostate cancer cells is dramatically reduced in comparison to cells derived from normal of benign prostatic hyperplasia (page 68, 1st column, 2nd paragraph). Similarly, Hsu et al. (Cancer Research 2001; 61: 2852-2856) quantified the levels of endogenous 1a-hydroxylase activity in a series of primary cultures of human prostatic epithelial cells derived from normal tissue, BPH, adenocarcinomas and several prostatic CA cell lines (page 2852, 2nd column, 3rd paragraph). Specifically, Hsu et al. found that CA cells had approximately 10 to 20

fold lower levels of 1 a-hydroxylase activity compared with cells from normal tissues (page 2852, 2nd column, 3rd paragraph). Likewise, Whitlatch et al. (J. Steroid Biochem. Molecular Biology 2002; 81: 135-140) compared the levels of 1a-OHase activity in prostate cancer cell lines, LNCaP, DU145 and PC-3 and in primary cultures of normal, cancerous and benign prostatic hyperplasia (BPH) prostate cells (abstract). In particular, Whitlatch et al. observed that compared to primary cultures of normal prostate cells, primary cultures of prostate cancer cells and prostate cancer cell lines demonstrate a marked decline in 1a-OHase activity (page 138, 2nd column, last paragraph and page 137, Figure 1). As such, both Hsu et al. and Ma et al teach that the proposed strategy of using 25(OH)D3 as a therapeutic agent for prostate cancer will be ineffective (abstract or Hsu et al. and page 68, 1st column, 1st full paragraph of Ma et al.)

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or

malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-4, 7-8, 10-11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Raina et al. (Br. J. Cancer 1991; 63: 463-465) in view of Haussler et al. (JAMA 1982; 247: 841-844).

Raina et al. teach a method of treating progressive low grade non-hodgkin's lymphoma comprising administering 1 μg oral alfacalcidol daily (abstract). Thus, while Raina et al. do not explicitly teach that lymphoma have a hydroxylase enyzyme, e.g., 25-hydroxyvitmain D-1a-hydroxylase, for synthesizing 1,25-dihydroxyvitamin D, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure because the specification discloses (page 23, lines 11-24) that 1a-OHase is present in lymphoma cancer cells. , Moreover, although Pence et al. do not explicitly teach that alfacalcidol is metabolic precursor of 1,25-dihydroxyvitamin D, the claimed limitation appears to be an inherent property of the referenced method because as evidenced by Haussler et al., alfacalcidol is metabolized by the liver to 1,25(OH)2D3 (page 841, 3rd column, *Vitamin D Metabolism*). Hence, even though the claims are drawn to a mechanism by which 1,25-dihydroxyvitmain D is produced; the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claims 1, 3-4, 7-8, 10-11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Pence et al. (Carcinogenesis 1988; 9: 187-190) as evidenced by Hsu et al. (Cancer Research 2001; 61: 2852-2856).

Pence et al. teach a method of inhibiting colon tumor cells comprising administering a high enough dose of Vitamin D to inhibit growth, but a low enough dose to avoid toxicity from hypercalcemia (page 187, 2nd column and 189, 1st column, lines 2-5). Thus, while Pence et al. do not explicitly teach that the colon tumors cells have a hydroxylase enyzyme, e.g., 25-hydroxyvitmain D-1a-hydroxylase, for synthesizing 1,25-dihydroxyvitamin D, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure because the

specification discloses (page 25, lines 1-2) that colon or breast cells can respond to 1,25 (OH)2D due to their possessing 1a-OHase, e.g., 25-hydroxyvitmain D-1a-hydroxylase (Kitanaka, S. et al. N. Eng. J. Med. 1998; 338: 653-661). Moreover, although Pence et al. do not explicitly teach that vitamin D is metabolic precursor of 1,25-dihydroxyvitamin D, the claimed limitation appears to be an inherent property of the referenced method because as evidenced by Hsu et al. (Cancer Research 2001; 61: 2852-2856), Vitamin D3 undergoes sequential hydroxylation's, fist in the liver to form the relatively inactive circulating prohormone 25 (OH)D3 which is activated by 1a-hydroxlyase in the kidney to 1,25 (OH)2D3 (page 2852, 1st column, *Introduction*). Hence, even though the claims are drawn to a mechanism by which 1,25-dihydroxyvitmain D is produced, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pence et al. (Carcinogenesis 1988; 9: 187-190) as evidenced by Hsu et al. (Cancer Research 2001; 61: 2852-2856) in further view of Haussler et al. (JAMA 1982; 247: 841-844).

Pence et al. teach, as applied to claims 1, 3-4, 7-8, 10-11 and 14 above, a method of inhibiting colon tumor cells comprising administering a high enough dose of Vitamin D to inhibit growth, but a low enough dose to avoid toxicity from hypercalcemia (page 187, 2nd column and 189, 1st column, lines 2-5).

Pence et al. does not explicitly teach that the administration of 25-hydroxyvitamin D as the metabolic precursor.

Hausslet et al. teach that while calcitriol is the most active natural metabolite of Vitamin D, analogs such as calcifediol (25-hydroxyvitamin D) are safe and effective alternative therapeutic agents to Vitamin D (abstract). Specifically, the reference teaches that calcifediol has become a useful alternative to Vitamin D because it is faster acting and assays for measuring its concentration are readily available such that its therapeutic levels can be easily monitored (page 843, 2nd column, *Calcifediol*).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute Vitamin D as taught by Pence for 25-hydroxyvitamin D in view of Haussler et al. teachings that calcifediol, e.g., 25-hydroxyvitamin D, is recognized as a safe and effective alternative to Vitamin D. Moreover, one would have bee motivated because as taught by Haussler, calcifediol is faster acting than vitamin D and its therapeutic levels can be easily monitored by readily available techniques. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering 25-hydroxyvitamin D, one would achieve a safe and effective alternative to Vitamin D for the treatment of colon cancer.

Therefore, No clam is allowed.

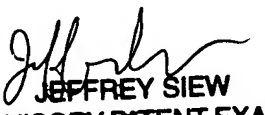
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF
June 5, 2006



JEFFREY SIEW
SUPERVISORY PATENT EXAMINER